



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/435, 9/48, 9/20</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/45924</b> <b>(43) International Publication Date:</b> 16 September 1999 (16.09.99)
<b>(21) International Application Number:</b> PCT/EP99/01557 <b>(22) International Filing Date:</b> 5 March 1999 (05.03.99)  <b>(30) Priority Data:</b> 60/077,527 11 March 1998 (11.03.98) US 9805192.3 11 March 1998 (11.03.98) GB 60/077,480 11 March 1998 (11.03.98) US  <b>(71) Applicants (for all designated States except US):</b> SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GLINECKE, Robert [US/US]; SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406 (US). MILOSOVICH, Susan, Marie [US/US]; SmithKline Beecham Pharmaceuticals, 1250 South Collegeville Road, Collegeville, PA 19426-0989 (US). MULDOON, William [US/US]; SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406 (US). ROUSSEAU, Laurence [FR/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third		Avenue, Harlow, Essex CM19 5AW (GB). SAUER, Joseph [US/US]; SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406 (US).  <b>(74) Agent:</b> VALENTINE, Jill, Barbara; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> COMPOSITION  <b>(57) Abstract</b>  Controlled release dosage forms useful in the treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## COMPOSITION

The present invention relates to novel formulations, and to their use in the treatment and/or prophylaxis of certain disorders.

5 [R-(Z)]- $\alpha$ -(methoxyimino)- $\alpha$ -(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) and methods for its preparation are disclosed in EP-A-0392803, WO95/31456 and WO93/17018. The compound enhances acetylcholine function via an action at muscarinic receptors within the central nervous system, and is therefore of potential use in the treatment and/or prophylaxis  
10 of dementia in mammals.

WO96/12486 discloses the use of compound X in the manufacture of a medicament for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease.

15 Fast-release swallow tablet and oral solution formulations of compound X both result in rapid absorption of the compound into the circulation, and require twice a day dosing for optimal efficacy.

It has now been surprisingly found that it is possible to formulate compound X, which has very high water solubility and is active at extremely low doses, in such  
20 a way that release is controlled to take place over a period of hours. Such a formulation would require dosing only once a day: this is likely to improve compliance in a patient population characterised by poor memory; it may also reduce side-effects in case of accidental overdosing.

25 Accordingly, in a first aspect the present invention provides a controlled release oral dosage form containing 0.04 %w/w pfb compound X and 98.5-99.5%w/w total mono, di and triglycerides and polyethylene glycol mono and diesters consisting of Gelucire 50/13 (EP) and Gelucire 50/02 (Fr Ph) in a ratio of >0.02 Gelucire 50/13 (EP) to Gelucire 50/02 (Fr Ph), in a hard gelatin capsule  
30 containing 0.10 mg/capsule compound X pfb, such that the release profile of the capsule in 1mM HCl is 20-60% after 8hr.

Preferably the release profile after 8hr is 20-40% or 30-60%.

Gelucire 50/13 (EP) is a mixture of mono, di and triglycerides and polyethylene glycol mono and diesters specified in the European Pharmacopeia  
35 "Stearoyl Macroglycerides" (Supplement 1998) as:

specific mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols with a mean relative molecular mass between 300 and 4000 comprising:

- free glycerol content: < 3%
  - 5 lauric acid (C12): < 5%
  - myristic acid (C14): < 5%
  - different nominal amounts of stearic acid (C18) and of palmitic acid (C16).
- The sum of stearic acid and of palmitic acid is not less than 90%.

- Gelucire 50/02 (Fr Ph) is a mixture of mono, di and triglycerides and
- 10 polyethylene glycol mono and diesters specified in the French Pharmacopoeia "Glycerides Polyglycolyses Satures" (1990) as:
- specific mixtures of mono, di and triglycerides and polyethylene glycol mono and diesters, obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging 200-2000, or by
- 15 esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging 200 -2000, comprising:

- free glycerol content: < 3%
- caprylic acid (C8): < 15%
- capric acid (C10): < 15%
- 20 lauric acid (C12): < 50%
- myristic acid (C14): < 25%
- palmitic acid (C16): < 55%
- stearic acid (C18): < 97%

- The mono, di and triglycerides and polyethylene glycol mono and diesters
- 25 preferably make up 99.41% of the dosage form. The ratio of Gelucire 50/13 (EP) to Gelucire 50/02 (Fr Ph) is preferably <0.055, more preferably  $\leq 0.053$ .

- In a preferred aspect the mixture of mono, di and triglycerides and polyethylene glycol mono and diesters consists of Gelucire 50/13 (Gattefosse) and Gelucire 50/02 (Gattefosse). Most preferably the composition comprises 97.41%
- 30 Gelucire 50/13 (Gattefosse) and 2.00% Gelucire 50/02 (Gattefosse) or 94.41% Gelucire 50/13 (Gattefosse) and 5.00% Gelucire 50/02 (Gattefosse).

The composition preferably additionally comprises propylene glycol, preferably at 0.45% w/w (1.13mg/capsule).

- The composition preferably additionally comprises 3,4,5-
- 35 trihydroxybenzoic acid propyl ester, preferably at 0.10% w/w (0.25mg/capsule).

In a preferred embodiment of the first aspect the composition is selected

from:

	Component	% w/w	mg/capsule
	Compound X	0.04 pfb	0.10 pfb
5	Gelucire 50/02 (EP)	94.41	236.00
	Gelucire 50/13 (Fr Ph)	5.00	12.50
	propylene glycol	0.45	1.13
	3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

10

and

	Component	% w/w	mg/capsule
	Compound X	0.04 pfb	0.10 pfb
15	Gelucire 50/02 (EP)	97.41	243.52
	Gelucire 50/13 (Fr Ph)	2.00	5.00
	propylene glycol	0.45	1.13
	3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

20

in a hard gelatin capsule.

In a second aspect, the present invention provides a controlled release oral dosage form containing compound X of the following composition:

25

	Ingredient	mg/tablet	%/tablet
	Compound X	0.005-0.1pfb	
	hydroxypropyl methylcellulose	37.5 - 45	25 - 30
	dibasic calcium phosphate dihydrate	45 - 52.5	30 - 35
30	microcrystalline cellulose		
	(nominal mean particle size 50 microns)	19.5	13.0
	microcrystalline cellulose		
	(nominal mean particle size 100 microns)	37.76	25.2

35 granulated, compressed into tablets and coated to a 3% weight gain with a seal coat consisting of a solution of hydroxypropyl methylcellulose aqueous dispersion with plasticizer in purified water at 10% solids followed by a coat consisting of

ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polyethylene glycol plasticizer, such that 40-65% of the drug is released within 8 hours in water.

The composition preferably additionally comprises:  
sodium dihydrogen citrate, preferably at a level of 1.50mg/tablet (1.0%) and/or magnesium stearate, preferably at a level of 1.125mg/tablet (0.75%).

In preferred embodiments of the second aspect:  
hydroxypropyl methylcellulose is Methocel E4M CR;  
microcrystalline cellulose (nominal mean particle size 50 microns) is Avicel PH101;  
microcrystalline cellulose (nominal mean particle size 100 microns) is Avicel PH102;  
hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and is preferably Opadry White or Opadry Clear (YS-1-9025A); and/or ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer and is preferably Surelease Clear (E-7-19010).

In a third aspect, the present invention provides a controlled release oral dosage form containing compound X of the following composition:

Ingredient	mg/tablet	%/tablet
Compound X	0.005-0.1pfb	
ethylcellulose	22.5 - 37.5	15 - 25
dibasic calcium phosphate dihydrate	63.3 - 78.3	42.2-52.2
microcrystalline cellulose	30.0-40.0	19.8-26.7

compressed into tablets and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and and hydroxypropylmethylcellulose aqueous dispersion with plasticizer.

In one preferred embodiment of the third aspect the composition additionally comprises sodium dihydrogen citrate, preferably at a level of 3.00mg/tablet (2.0%) and/or colloidal silicon dioxide, preferably at a level of 0.75mg/tablet (0.50%)

and/or magnesium stearate, preferably at a level of 1.125mg/tablet (0.75%) and/or the microcrystalline cellulose has a mean particle size of 100 microns, preferably at a level of 32.5mg/tablet (21.7%); and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polyethylene glycol plasticizer, such that 35 - 50 % of the drug is released within 8 hours in water.

In a second preferred embodiment of the third aspect the composition is wet granulated before compression using an ethyl cellulose aqueous dispersion containing oleic acid, ammonium hydroxide and plasticizer, preferably at a level of 7.5-15.0mg/tablet (5.0 - 10.0%). Where the composition is wet granulated, it additionally comprises sodium dihydrogen citrate, preferably at a level of 1.50mg/tablet (1.0%), and/or magnesium stearate, preferably at a level of 1.125mg/tablet (0.75%), and/or the microcrystalline cellulose has a mean particle size of 50 microns, preferably at a level of 37.5mg/tablet (25%); and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with plasticizer such that 60-75% of the drug is released within 8 hours in water.

In preferred embodiments of the third aspect:

ethylcellulose is Ethocel Std 7;

microcrystalline cellulose (nominal mean particle size 50 microns) is Avicel PH101;

microcrystalline cellulose (nominal mean particle size 100 microns) is Avicel PH102;

hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and is preferably Opadry Clear (YS-1-9025A); and/or

ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer and is preferably Surelease Clear (E-7-19010).



By controlled release is meant release of the active substance from the dosage form is modified to occur at a slower rate than that from an immediate release product, such as a conventional swallow tablet or capsule.

The dosage form of the invention may be used in the treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease. These disorders are herein after referred to as "the Disorders".

The present invention provides a method of treating "the Disorders" by administering an effective amount of the controlled release oral dosage form of the invention to a sufferer in need thereof.

The present invention further provides the use of a controlled release oral dosage form of the invention in the manufacture of a medicament for treating "the Disorders".

The present invention also provides a pharmaceutical composition for use in the treatment of "the Disorders" which comprises a controlled release oral dosage form of the invention.

The following example illustrates the present invention. The weight shown is the weight of free base (pfb = pure free base). Mesh sizes are US standard.

20

**Example 1**

Component	% w/w	mg/capsule	Function
Compound X	0.04 pfb	0.10 pfb	Active
Gelucire 50/02*	94.41	236.00	Wax matrix
25 Gelucire 50/13*	5.00	12.50	Wax matrix
propylene glycol	0.45	1.13	Solvent
propyl gallate**	0.10	0.25	Antioxidant

**Example 2**

Component	% w/w	mg/capsule	Function
Compound X	0.04 pfb	0.10 pfb	Active
Gelucire 50/02*	97.41	243.52	Wax matrix
Gelucire 50/13*	2.00	5.00	Wax matrix
propylene glycol	0.45	1.13	Solvent
35 propyl gallate**	0.10	0.25	Antioxidant

\*specific mixture of mono, di and triglycerides, and polyethylene glycol mono and diesters of the following compositions:



Gelucire 50/13 (Gattefosse, certificate of analysis):

- Free glycerol content: < 3%
- Caprylic acid: < 3%
- Capric acid: < 3%
- 5 Lauric acid: < 5%
- Myristic acid: < 5%
- Palmitic acid: 40-50%
- Stearic acid: 48-58%

10 Gelucire 50/02 (Gattefosse, certificate of analysis):

- Free glycerol content: < 3%
- Caprylic acid: < 3%
- Capric acid: < 3%
- Lauric acid: 4-14%
- 15 Myristic acid: 2-12%
- Palmitic acid: 32-42%
- Stearic acid: 37-47%

\*\*3,4,5-trihydroxybenzoic acid propyl ester

20

**Process for Examples 1 and 2:**

Waxes were melted together at around 60 degrees C and mixed with propyl gallate. Compound X was dissolved in propylene glycol, and blended into the waxes. The mixture was filled into size 3 hard gelatin capsule shells.

25

**Release profiles**

Dissolution equipment conforming to an apparatus No.2 of USP.

Medium: 1 mM HCl.

30 Volume: 500 mL

Temperature: 37C.

Paddle speed: 50rpm.

Table 1.: Release Profile of wax-filled capsules of Example 1

Time (hr)	% Released
2	17
4	27
8	46
15	70
23	86

Table 2.: Release Profile of wax-filled capsules of Example 2

Time (hr)	% Released
2	10
4	18
8	29
15	44
23	56

**Example 3**

	Ingredient	mg/tablet	Function
10	Compound X	0.005-0.1pfb	Active
	Methocel E4M CR	37.5	Hydrogel matrix
	sodium dihydrogen citrate	1.50	Stabilizer
	dibasic calcium phosphate dihydrate	52.5	Hydrophobic diluent
	Avicel PH101	19.5	Hydrophobic diluent
15	Avicel PH102	37.76	Hydrophobic diluent
	magnesium stearate	1.125	Lubricant
	purified water	q.s.	

Tablets were prepared by the following procedure:

- 20 1. Preblend the drug with a small quantity of the excipients
2. Wet granulate using high shear granulation
3. Dry granulation using fluid bed or oven process
4. Screen through a comminuting mill
5. Blend the remaining excipients with the drug granulation
- 25 6. Lubricate with magnesium stearate

7. Compress into tablets
8. Coat tablets with polymer

**Seal coating solution:**

- 5           A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations was made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

**Polymer Coating:**

- 10           A polymer coating dispersion containing ethylcellulose (Surelease Clear (E-7-19010)) and Opadry Clear (YS-1-9025A) of the following composition was made and used for polymer coating the seal coated beads at 4-5% weight gain.

	Component	% w/w	Function
15	Surelease Clear (E-7-19010)	4.5 (25% as solids)	Release controlling polymer coat with plasticiser
	Opadry Clear(YS-1-9025A)	0.5	Release controlling polymer coat
	Purified water	q.s.	
20	Total	100	

- 25           700 grams of core tablets were coated using a Vector LDCS pan to a 3% weight gain with the Opadry Clear (YS-1-9025A) seal coating solution. The seal coated tablets were then polymer coated to 4-5% weight gain using the Surelease/Opadry coating dispersion.

Table 3. Release Profile for tablet of Example 3 of Compound X in water

Time (hr)	% Dissolved	
	4% coat	5% coat
1	0.14	0.17
2	0.61	0.35
4	19.9	6.6
8	62	52
12	87	92

**Example 4**

	<b>Ingredient</b>	<b>mg/tablet</b>	<b>Function</b>
	Compound X	0.005-0.1pfb	Active
	Ethocel Std 7	30.0	Hydrogel matrix
5	sodium dihydrogen citrate	1.50	Stabilizer
	dibasic calcium phosphate dihydrate	70.76	Hydrophobic diluent
	Avicel PH101	37.5	Hydrophobic diluent
	Surelease Clear (E-7-19010)	9.0	Hydrogel matrix
	magnesium stearate	1.125	Lubricant

10

Tablets were prepared by the following procedure:

1. Preblend the drug with a small quantity of the excipients
2. Granulate mix with Surelease dispersion using high shear granulation and wet screen resulting granulation
- 15 3. Dry granulation using fluid bed
4. Screen through a sizing mill
5. Blend the remaining excipients with the drug granulation
6. Lubricate with magnesium stearate
7. Compress into tablets
- 20 8. Coat tablets with polymer

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations was made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

25

Polymer Coating: A polymer coating dispersion containing ethylcellulose (Surelease (E-7-19010) and Opadry Clear (YS-1-9025A) of the following composition was made and used for polymer coating the seal coated tablets at 4-5% weight gain.

30

<b>Component</b>	<b>% w/w</b>	<b>Function</b>
Surelease Clear (E-7-19010)	4.25 (25% as solids)	Release controlling polymer coat with plasticiser
Opadry Clear (YS-1-9025A)	0.75	Release controlling polymer coat
35 purified water	q.s.	
Total	100	

700 grams of core tablets were coated using a Vector LDCS pan to a 3% weight gain with the Opadry Clear seal coating solution. The seal coated tablets were then polymer coated to 4-5% weight gain using the Surelease/Opadry coating dispersion.

5

Table 4. Release Profile for the tablet of Example 4 of Compound X in water

Time (hr)	% Dissolved	
	4% coat	5% coat
1	2.1	0.57
2	7.4	3.1
4	35	26
8	73	71
12	90	88

#### Example 5

	Ingredient	mg/tablet	Function
10	Compound X	0.005-0.1pfb	Active
	Ethocel Std 7	37.5	Hydrogel matrix
	sodium dihydrogen citrate	3.00	Stabilizer
	dibasic calcium phosphate dihydrate	75.0	Hydrophobic diluent
	Avicel PH102	32.5	Hydrophobic diluent
15	colloidal silicon dioxide	0.75	Glidant
	magnesium stearate	1.125	Lubricant

Tablets were prepared by the following procedure:

1. Preblend the drug with a small quantity of the excipients
  - 20 2. Blend the remaining excipients with the drug preblend
  3. Lubricate with magnesium stearate
  4. Compress into tablets
  5. Coat tablets with polymer
- 25 Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations was made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

Polymer Coating: A polymer coating dispersion containing ethylcellulose  
 30 (Surelease (E-7-19010)) and Opadry Clear (YS-1-9025A) of the following

composition was made and used for polymer coating the seal coated tablets at 4% weight gain.

	Component	% w/w	Function
5	Surelease Clear (E-7-19010)	3.4 (25% as solids)	Release controlling polymer coat with plasticiser
	Opadry Clear (YS-1-9025A)	0.6	Release controlling polymer coat
	purified water	q.s.	
10	Total	100	

700 grams of core tablets were coated using a Vector LDCS pan to a 3% weight gain with the Opadry Clear seal coating solution. The seal coated tablets were then polymer coated to 4% weight gain using the Surelease/Opadry coating dispersion.

15

Table 5. Release Profile for tablet of Example 5 of Compound X in water

Time (hr)	% Dissolved
2	6.2
4	14
8	38
12	66
16	90

	Tradename	Generic description	Supplier
5	Ethocel Std 7	ethylcellulose (viscosity 5%w/v solution of 6.4 mPa mean particle size 210microns)	Dow
10	Methocel E4M CR	hydroxypropyl methcellulose (nominal viscosity, 2% in water, of 4000) %methoxyl=28-30, 95%<100 mesh)	Dow
	Avicel PH101	microcrystalline cellulose (nominal mean particle size 50 microns)	FMC Corp
15	Avicel PH102	microcrystalline cellulose (nominal mean particle size 100 microns)	FMC Corp
	Opadry Clear (YS-1-9025A)	hydroxymethylcellulose aqueous dispersion with polyethylene glycol plasticizer	Colorcon
20	Surelease Clear (E-7-19010)	aqueous dispersion of ethyl cellulose oleic acid ammonium hydroxide fractionated coconut oil plasticizer	Colorcon
25			



**CLAIMS**

1. A controlled release oral dosage form containing [R-(Z)]- $\alpha$ -(methoxyimino)- $\alpha$ -(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) of the following composition:

5	<b>Ingredient</b>	<b>mg/tablet</b>	<b>%/tablet</b>
	Compound X	0.005-0.1pfb	
	ethylcellulose	22.5 - 37.5	15 - 25
	dibasic calcium phosphate dihydrate	63.3 - 78.3	42.2-52.2
	microcrystalline cellulose	30.0-40.0	19.8-26.7

10

compressed into tablets and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and and hydroxypropylmethylcellulose aqueous dispersion with plasticizer.

15

2. A dosage form according to claim 1 which additionally comprises sodium dihydrogen citrate and/or colloidal silicon dioxide and/or magnesium stearate and/or the microcrystalline cellulose has a mean particle size of 100 microns; and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polythylene glycol plasticizer, such that 35 - 50 % of the drug is released within 8 hours in water.

20

25

3. A dosage form according to claim 2 which comprises sodium dihydrogen citrate at a level of 3.00mg/tablet (2.0%) and/or colloidal silicon dioxide at a level of 0.75mg/tablet (0.50%) and/or magnesium stearate at a level of 1.125mg/tablet (0.75%) and/or microcrystalline cellulose at a level of 32.5mg/tablet (21.7%).

30

4. A dosage form according to claim 1 wherein the composition is wet granulated before compression using an ethyl cellulose aqueous dispersion containing oleic acid, ammonium hydroxide and plasticizer.

5. A dosage form according to claim 4 wherein the ethyl cellulose dispersion is at a level of 7.5-15.0mg/tablet (5.0 - 10.0%).

35

6. A dosage form according to claim 4 or 5 which additionally comprises sodium dihydrogen citrate and/or magnesium stearate and/or the micorcrystalline

cellulose has a mean particle size of 50 microns; and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with plasticizer such that 60-75% of the drug is released within 8 hours in water.

7. A dosage form according to claim 6 which comprises sodium dihydrogen citrate at a level of 1.50mg/tablet (1.0%) and/or magnesium stearate at a level of 1.125mg/tablet (0.75%) and/or microcrystalline cellulose at a level of 37.5mg/tablet (25%).

8. A dosage form according to any one of claims 1 to 7 wherein the hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and/or the ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer.

9. A controlled release oral dosage form according to claim 1 of the following composition:

	Ingredient	mg/tablet
20	Compound X	0.005-0.1pfb
	Ethocel Std 7	30.0
	sodium dihydrogen citrate	1.50
	dibasic calcium phosphate dihydrate	70.76
	Avicel PH101	37.5
25	Surelease Clear (E-7-19010)	9.0
	magnesium stearate	1.125

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations made by dissolving 100 grams of Opadry Clear into 900 grams of purified water (to 3% weight gain);

Polymer Coating: (4-5% weight gain)

	Component	% w/w
	Surelease Clear (E-7-19010)	4.25 (25% as solids)
35	Opadry Clear (YS-1-9025A)	0.75
	purified water	q.s.
	Total	100.

10. A controlled release oral dosage form according to claim 1 of the following composition:

	Ingredient	mg/tablet	Function
5	Compound X	0.005-0.1pfb	Active
	Ethocel Std 7	37.5	Hydrogel matrix
	sodium dihydrogen citrate	3.00	Stabilizer
	dibasic calcium phosphate dihydrate	75.0	Hydrophobic diluent
	Avicel PH102	32.5	Hydrophobic diluent
10	colloidal silicon dioxide	0.75	Glidant
	magnesium stearate	1.125	Lubricant

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations made by dissolving 100 grams of Opadry Clear into  
 15 900 grams of purified water (to 3% weight gain);

Polymer Coating: (4% weight gain):

	Component	% w/w
	Surelease Clear (E-7-19010)	3.4 (25% as solids)
20	Opadry Clear (YS-1-9025A)	0.6
	purified water	q.s.
	Total	100.

11. A controlled release oral dosage form containing [R-(Z)]- $\alpha$ -(methoxyimino)-  
 25  $\alpha$ -(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) of the following composition:

	Ingredient	mg/tablet	%/tablet
	Compound X	0.005-0.1pfb	
	hydroxypropyl methylcellulose	37.5 - 45	25 - 30
30	dibasic calcium phosphate dihydrate	45 - 52.5	30 - 35
	microcrystalline cellulose		
	(nominal mean particle size 50 microns)	19.5	13.0
	microcrystalline cellulose		
	(nominal mean particle size 100 microns)	37.76	25.2

35

granulated, compressed into tablets and coated to a 3% weight gain with a seal coat consisting of a solution of hydroxypropyl methylcellulose aqueous dispersion with

plasticizer in purified water at 10% solids followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polyethylene glycol plasticizer, such that 40-65% of the drug is released within 8 hours in water.

12. A dosage form according to claim 11 which additionally comprises: sodium dihydrogen citrate and/or magnesium stearate.

13. A dosage form according to claim 12 which comprises sodium dihydrogen citrate at a level of 1.50mg/tablet (1.0%) and/or magnesium stearate at a level of 1.125mg/tablet (0.75%)

14. A dosage form according to any one of claims 11 to 13 wherein the hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and/or the ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer.

15. A controlled release oral dosage form according to claim 11 of the following composition:

Ingredient	mg/tablet
Compound X	0.005-0.1pfb
20 Methocel E4M CR	37.5
sodium dihydrogen citrate	1.50
dibasic calcium phosphate dihydrate	52.5
Avicel PH101	19.5
Avicel PH102	37.76
25 magnesium stearate	1.125
purified water	q.s.

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

30 Polymer Coating (4-5% weight gain):

Component	% w/w
Surelease Clear (E-7-19010)	4.5 (25% as solids)
Opadry Clear(YS-1-9025A)	0.5
Purified water	q.s.
35 Total	100

16. A controlled release oral dosage form containing 0.04 %w/w pfb [R-(Z)]- $\alpha$ -(methoxyimino)- $\alpha$ -(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) and 98.5-99.5%w/w total mono, di and triglycerides and polyethylene glycol mono and diesters consisting of Gelucire 50/13 (EP) and
- 5 Gelucire 50/02 (Fr Ph) in a ratio of >0.02 Gelucire 50/13 (EP) to Gelucire 50/02 (Fr Ph), in a hard gelatin capsule containing 0.10 mg/capsule compound X pfb, such that the release profile of the capsule in 1mM HCl is 20-60% after 8hr.
17. A dosage form according to claim 16 wherein the release profile after 8hr is 20-40% or 30-60%.
- 10 18. A dosage form according to claim 16 or 17 which comprises 97.41% Gelucire 50/13 and 2.00% Gelucire 50/02 or 94.41% Gelucire 50/13 and 5.00% Gelucire 50/02.
19. A dosage form according to any of claims 16 to 18 which additionally comprises propylene glycol.
- 15 20. A dosage form according to claim 19 which comprises propylene glycol at 0.45% w/w.
21. A dosage form according to any of claims 16 to 20 which additionally comprises 3,4,5-trihydroxybenzoic acid propyl ester.
22. A dosage form according to claim 21 which comprises 3,4,5-
- 20 trihydroxybenzoic acid propyl ester at 0.10% w/w.
23. A dosage form according to any of claims 16 to 22 which comprises 0.04% pfb w/w compound X.
24. A dosage form according to claim 16 selected from:
- | Component               | % w/w    | mg/capsule |
|-------------------------|----------|------------|
| 25 Compound X           | 0.04 pfb | 0.10 pfb   |
| Gelucire 50/02 (EP)     | 94.41    | 236.00     |
| Gelucire 50/13 (Fr Ph)  | 5.00     | 12.50      |
| propylene glycol        | 0.45     | 1.13       |
| 3,4,5-trihydroxybenzoic |          |            |
| 30 acid propyl ester    | 0.10     | 0.25       |
- and

	<b>Component</b>	<b>% w/w</b>	<b>mg/capsule</b>
	Compound X	0.04 pfb	0.10 pfb
	Gelucire 50/02 (EP)	97.41	243.52
	Gelucire 50/13 (Fr Ph)	2.00	5.00
5	propylene glycol	0.45	1.13
	3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

in a hard gelatin capsule.

10

25. A process for preparing a dosage form as defined in any one of claims 1 to 24 which process comprises admixing the ingredients.

26. A method of treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease by administering an effective amount of the dosage form of any one of claims 1 to 24 to a sufferer in need thereof.

27. The use of a dosage form of any one of claims 1 to 24 in the manufacture of a medicament for treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease.

28. A pharmaceutical composition for use in the treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease which comprises a dosage form of any one of claims 1 to 24.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/01557

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/435 A61K9/48 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 04750 A (SMITHKLINE BEECHAM PLC ;NAPPER JAMES ALBERT (GB); MORTIMER NEIL (G) 13 February 1997 (1997-02-13) page 1, line 3 - line 6 page 5 - page 6, column 1 ---	1-24
A	WO 96 12486 A (SMITHKLINE BEECHAM PLC ;MARKWELL ROGER EDWARD (GB); HAWKINS JULIE) 2 May 1996 (1996-05-02) cited in the application page 2, line 18 - line 29 ---	1-24
P, A	WO 98 10762 A (NAPPER JAMES ALBERT ;ROUSSEAU LAURENCE (GB); SMITHKLINE BEECHAM PL) 19 March 1998 (1998-03-19) the whole document -----	1-24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

19 August 1999

Date of mailing of the international search report

26/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01557

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9704750 A	13-02-1997	AU 6738496 A	26-02-1997
		BG 102266 A	30-10-1998
		CA 2228048 A	13-02-1997
		CN 1196677 A	21-10-1998
		CZ 9800247 A	17-06-1998
		EP 0841902 A	20-05-1998
		HU 9900521 A	28-06-1999
		NO 980384 A	26-03-1998
		PL 325242 A	06-07-1998
		SK 11098 A	08-07-1998
WO 9612486 A	02-05-1996	AU 698695 B	05-11-1998
		AU 3843195 A	15-05-1996
		BG 101500 A	30-01-1998
		BR 9509433 A	16-09-1997
		CN 1170365 A	14-01-1998
		CZ 9701251 A	16-07-1997
		EP 0786998 A	06-08-1997
		HU 77007 A	02-03-1998
		JP 10509697 T	22-09-1998
		NO 971899 A	24-04-1997
		SK 50497 A	10-09-1997
		US 5891887 A	06-04-1999
		ZA 9508946 A	20-08-1996
WO 9810762 A	19-03-1998	AU 4128897 A	02-04-1998
		EP 0929301 A	21-07-1999
		NO 991194 A	11-03-1999